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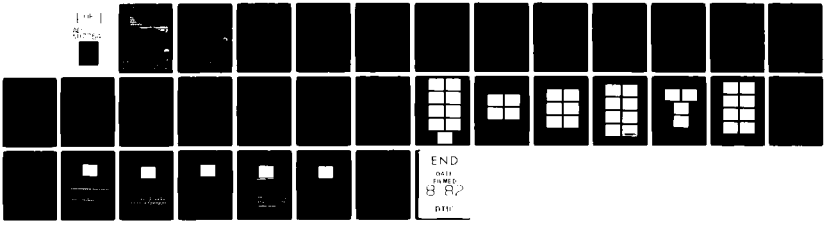

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THE ELECTROPHYSIOLOGIC MECHANISMS OF HALOGENATED ALKANE ARRHYTHMOGENESIS

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20. ABSTRACT (Continue on reverse side if necessary and identify by block number)

Bromochlorodifluoromethane (1211) has been shown to sensitize the myocardium to the arrhythmogenic effects of various adrenergic amines. The effects of certain physiologic and pharmacologic interventions were tested, including stretching of the tissue fiber, alpha adrenergic interactions, cyclic adenosine monophosphate interactions and beta blockade of slow ion channel stimulation. Other studies indicate that 1211 has no apparent direct arrhythmogenic action on the dog heart, but acts only to sensitize the heart to adrenergic amines. Present studies indicate that 1211, like beta adrenergic amines, elevates cellular

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20. Abstract (continued)

cyclic adenosine monophosphate levels which, through second messenger action, contributes to the alterations in cardiac membrane properties produced by these agents.

STATEMENT OF WORK

The work completed during the second contract year is a continuation of the work initiated during the first year in accordance with the objectives stated in the original proposal. Our efforts during this year were concentrated on the single compound, bromochlorodifluoromethane (1211) and included (I) the determination of various physiologic and pharmacologic interventions which influence the electrophysiologic characteristics of cardiac rhythm disturbances produced by 1211 and adrenergic amines; (II) *in vivo* dog experiments to establish what, if any, effects on the cardiac rhythm are due solely to 1211, i.e., without concommitant adrenergic influence; (III) blood superfusion experiments to relate cellular membrane alterations to whole animal arrhythmia production; and (IV) the role of cyclic AMP in cardiac arrhythmias due to the interaction of 1211 and adrenergic amines.

STATUS OF RESEARCH

I. Physiologic and Pharmacologic Modification of 1211 Membrane Effects

Fiber stretch experiments

In an effort to simulate the effects of increased blood pressure and, hence, increased afterload which produces stretch in the ventricular wall, Purkinje fibers were stretched 20% beyond their relaxed length and exposed to various concentrations of 1211 (Fig. 1). In the paced fiber, stretching alone had little effect on the action potential configuration or other parameters. However, with the application of 1211, the rate of upstroke, overshoot and duration were all reduced, giving the Purkinje fiber action potential the

appearance of a ventricular muscle action potential. In the spontaneously beating fiber, stretch can be seen to increase the intrinsic rate which is further enhanced when 1211 is again applied.

Alpha stimulation by phenylephrine

Realizing that alpha receptors exist in the myocardium, though relegated to a minor role in comparison to beta receptor regulation, it was important to determine how 1211 might interact with alpha stimulation (endogenously released epinephrine is both alpha and beta). In a manner similar to the sensitization experiments with the pure beta stimulant, isoproterenol, the response to various concentrations of phenylephrine was determined with and without 1211 (Fig. 2). Phenylephrine at the applied concentrations, is a pure alpha agonist; the alpha effects of epinephrine in the heart are masked by the dominant beta effects. It is apparent from these results that doses of phenylephrine in the range of 10^{-9} M to 10^{-7} M produce practically no change in action potential configuration or other characteristics. This may result from the paucity of alpha receptors in the ventricle. Phenylephrine causes a slight increase in action potential duration which is not potentiated by 1211, but rather the combined effects are additive in that the net results are a summation of shortening due to 1211 and the prolongation due to phenylephrine. This apparent lack of alpha adrenergic potentiation by 1211 is not surprising because such action has not been reported for other sensitizing halogenated alkanes.

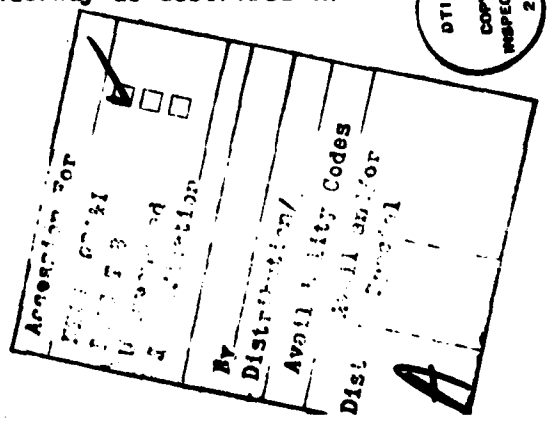
Interaction of cyclic AMP and 1211

Cyclic adenosine monophosphate (cAMP) acts as a second messenger in response to beta adrenergic stimulation in the heart and elsewhere. That

cAMP and the system that regulates it mediate cardiac membrane effects is well-established. Because the interaction between 1211 and beta adrenergic stimulation to sensitize the heart may be mediated via the cAMP system, several experiments to determine this have been performed.

The effects of inhibiting phosphodiesterase, the enzyme responsible for the removal of cAMP, have been reported previously. Briefly, inhibition of this enzyme by aminophylline, while stimulating adenyl cyclase through the beta receptor with isoproterenol coupled with exposure to 1211 produced greater changes in cardiac membrane effects than did any two of these treatments alone. This suggests a common effect which may be stimulation of cAMP.

A second approach to determine cAMP relationship to cardiac sensitization was the application of dibutyryl cAMP. This compound is permeable to the cardiac membrane (the parent compound is not) and once inside the cell, it is probably converted to the monobutyryl compound and cAMP. Once inside the cell, cAMP acts on various sites, such as the endogenously stimulated release might. To test whether the effects of dibutyryl cAMP might be enhanced by 1211, experiments of the type depicted in Fig. 3 were performed. As can be seen, successively increasing amounts of dibutyryl cAMP produce changes in the action potential configuration, including duration and refractoriness as well as enhancement of spontaneous automaticity. This is not unlike beta stimulation due to isoproterenol. 1211 augments the membranes' effects of dibutyryl cAMP, suggesting again a role for this second messenger in cardiac sensitization. Additional work in this area is underway as described in Section IV.



Slow channel calcium-mediated action potential blockade by 1211

In order to examine the dose-dependent effects of 1211 on the slow channel plateau current, the tissue was depolarized by potassium and enriched with calcium (Fig. 4). Isoproterenol, by beta stimulation, caused an increased calcium current which is primarily responsible for the shortening of the action potential plateau. The slow inward calcium current was progressively diminished at increasing levels of 1211. The effect at the highest concentration was very similar to the blocking effect produced by atenolol, a beta blocker without intrinsic membrane stabilizing properties. Though the effects of 1211 and atenolol were similar, it is likely that the 1211 effect is directly on the membrane rather than at the receptor as with atenolol.

II. Cardiac Sensitization by 1211 in Conscious Dogs

This series of experiments was performed in order to define the conditions for cardiac sensitization to isoproterenol by 1211. The electrophysiology experiments in this study have employed isoproterenol, a beta adrenergic agonist, and the blood superfusion experiments, likewise, employ isoproterenol. Few, if any, animal studies with 1211 cardiac sensitization have been performed with isoproterenol, but rather with epinephrine or norepinephrine, alpha and beta adrenergic agonists. The use of isoproterenol in these experiments is justified because the extracardiac vasoconstriction is eliminated as well as possible alpha adrenergic cardiac effects (see phenylephrine experiments, this report). On the other hand, using epinephrine or norepinephrine more nearly reproduces the actual situation in which endogenously released catecholamines interact with 1211 in the sensitization process.

These experiments were conducted on conscious, but pancuronium-immobilized dogs. This was necessary for two reasons. First, when 1211 was administered to pentobarbital anesthetized animals, the arrhythmogenic level was excessively high when compared to previous reports with conscious animals. Second, when fully conscious, chronically tracheostomized dogs were made to breathe low levels (2%) of 1211, the initial response was a convulsive state which precluded continuation of monitoring for cardiovascular irregularities.

To conduct these conscious immobilized experiments, the animals were anesthetized briefly with sodium thiamylal and intubated with a cuffed endotracheal tube. In those experiments where blood pressure was monitored, the arterial catheter was introduced during the period of anesthesia and the site of insertion was anesthetized locally with xylocaine. Before recovery from anesthesia, the dogs were administered the neuromuscular blocker, pancuronium, at a dosage of 0.05 mg/kg. Respiration and the metered delivery of 1211 was maintained by a respirator.

In the first series of experiments,dogs were given progressively larger doses of isoproterenol until a ventricular rhythm disturbance occurred (defined minimally as three abnormal beats during any five second period). In Table I and Figure 5, the results of these experiments are presented. In all animals studied, a ventricular arrhythmia, as defined above, was not seen at 1 µg/kg, but developed at a level of 3 µg/kg. After exposure to 5% 1211 for five minutes, followed by progressively larger challenging doses of isoproterenol, all animals developed an arrhythmia at or below a dosage of 0.08 µg/kg of isoproterenol. This indicates cardiac sensitization at this level of exposure and provides a basis for the subsequent blood superfusion experiments.

In the second series of experiments,the objective was to determine whether 1211, by itself, would induce substantial changes in the cardiac membrane to cause arrhythmias. Evidence for a direct, intrinsic action by this compound on the cardiac action potential has already been reported. In Table II and Figure 6, the results of these experiments are presented. Atenolol, a pure beta I blocker, was administered at the rate of 4 mg/kg. Increasing concentrations of 1211, up to 20% of the inspired air, were administered. At each concentration, a challenging dose of 1 μg/kg of isoproterenol was given. At concentrations of 1211 up to 20% in the presence of complete beta blockade, no arrhythmia developed. With a dose of isoproterenol shown above to be arrhythmogenic in the sensitized heart, the beta blockade was not overcome until the highest concentration of 1211 was given. This suggests that despite previous reports as well as substantial direct membrane effects, 1211 is not arrhythmogenic in the absence of (or blockade of) endogenous adrenergic amines.

III. Blood Superfusion Experiments

Blood superfusion of isolated Purkinje fibers was performed in order to relate the cardiac membrane response to production of ventricular arrhythmias in the intact animal. A detailed description of the experimental procedure was presented in the original proposal. Briefly, Purkinje fibers from one dog's heart were mounted in the Tyrode's superfused tissue bath. A second dog was anesthetized and prepared to provide blood for superfusion of the isolated tissue. Blood pressure, left ventricular pressure and electrocardiograms were recorded from this dog and both 1211 and isoproterenol were

administered directly to the animal. Following equilibration with blood superfusion and the recording of normal parameters (Fig. 7), the animal was tested with several concentrations of isoproterenol to determine an arrhythmogenic dose. Following recovery, the animal was made to breathe a mixture of 1211 (5%) in air and challenged a second time with isoproterenol. The appearance of ventricular arrhythmias occurred at a lower level of isoproterenol when combined with 1211. Decreased refractoriness and slowed conduction were noted in the Purkinje action potential. Following beta blockade with atenolol, the same challenge of isoproterenol failed to produce any rhythm disturbance and was thus, protective. Continuing experiments with this model will compare epinephrine to isoproterenol and look at other possible interventions.

IV. Cyclic AMP Mediation of 1211-Adrenergic Amine Sensitization

Introduction

Isoproterenol, a beta I and II agonist, stimulates a concentration-dependent increase in automaticity and cyclic adenosine monophosphate (cAMP) concentration. Both of these effects are reduced when propranolol is administered. When intracellular phosphodiesterase inhibitors (such as aminophylline) are compared with epinephrine, a common mode of action is found: intracellular cAMP concentration. Phosphodiesterase inhibitors, which increase intracellular cAMP concentration by reducing the breakdown of cAMP, cause a voltage shift in the potassium (K^+) current similar to that caused by epinephrine. The effects of phosphodiesterase inhibitors are not blocked by beta adrenergic receptor blockers, although epinephrine K^+ channel effects are. It is possible that the magnitude of the K^+ channel voltage shift is

limited by saturation of a process "downstream" from the increased cAMP levels. Cyclic AMP concentration continues to increase when aminophylline, epinephrine, or both are administered even after the voltage shift has reached a maximum. This suggests that this saturable process downstream from cAMP may be either a protein kinase reaction which phosphorylates the inside of the membrane near the K^+ channel, or removal of calcium from binding sites near the channel by stimulation of calcium uptake by the sarcoplasmic reticulum (a process which is also dependent on cAMP-activated protein kinase.

It is possible that cyclic guanosine monophosphate (cGMP) may also play a role in regulating cardiac function. According to the Yin Yang Hypothesis, cAMP and cGMP may act antagonistically, or at times, synergistically to regulate certain systems (especially in the heart, platelets and smooth muscle).

Objectives

1. To evaluate the effects of 1211 on intracellular cAMP concentration in canine cardiac Purkinje fibers and to relate any cAMP effects to electrophysiological effects.

2. To relate proportional changes in cAMP:cGMP to changes seen in the Purkinje fiber action potential in the presence of 1211 (alone or in combination with certain drugs).

3. To localize the action of 1211 within the Purkinje fiber by process of elimination: alpha adrenergic receptor, beta adrenergic receptor, adenylate cyclase, phosphodiesterase, calcium.

Methods

The isolation, preparation and recording of electrophysiologic parameters from canine Purkinje fibers described previously will be followed. These parameters include:

Threshold voltage

Automaticity: escape time, spontaneous rate, slope of diastolic depolarization, activation voltage

Gate

Derivative of rapid depolarization (phase 0), dV/dt, $t_{1,2}$ and $t_{2,3}$ between impaled cells

Resting potential

Action potential amplitude and overshoot

Action potential duration at 25%, 50% and 90% replarization

Gas flows: O_2, CO_2 of bathing Tyrode's solution

pH of bathing Tyrode's solution

All Purkinje fibers will be subjected to the control period and measurements just described.

Pilot experiments may be performed to determine optional concentrations of isoproterenol and time course of drug effect on cyclic nucleotide concentration.

Experiment #1

It will be assumed here that each heart will supply three satisfactory Purkinje fibers. If fewer or more fibers are removed from any one heart, the procedure may be modified.

Purkinje Fiber #1: Control. No drugs or 1211 will be administered. After recording the action potential characteristics, the fiber will be carefully and quickly removed from the bath and prepared for cyclic nucleotide assay by immediate homogenation in cold trichloroacetic acid, then frozen.

Purkinje Fiber #2: 1211 alone. After recording the control action potential characteristics for this fiber, 40 μg/ml of 1211 will be administered. When a maximum effect due to 1211 is seen, or if maximum effect is difficult to determine after 20 minutes of 1211 exposure, the fiber will be quickly prepared for cyclic nucleotide assay as described for fiber #1.

Purkinje Fiber #3: Isoproterenol alone. After recording the control action potential characteristics for this fiber, enough isoproterenol will be added to the reservoir to produce a 10^{-6} M concentration in the bath. After making recordings and a maximum effect is seen, the fiber will be quickly prepared for cyclic nucleotide assay.

Whenever 1211 is bubbled into the bathing solution, samples will be extracted from the bath to test gas concentrations using a gas chromatograph.

Experiment #2

Fiber #1: Atenolol alone. After recording the control action potential characteristics for this fiber, a complete beta adrenergic receptor blocking dose of atenolol will be added to the tissue bath. When beta block is complete, the fiber will be prepared for assay.

Fiber #2: 1211,then isoproterenol.

Fiber #3: Atenolol, 1211,then isoproterenol

Experiment #3

Fiber #1: Aminophylline (complete phosphodiesterase blocking dose)

Fiber #2: Aminophylline, then 1211

Fiber #3: Aminophylline, then 1211, then 10^{-6} M isoproterenol

Experiment #4:

Fiber #1: Calcium-blocking dose of Verapamil alone

Fiber #2: Verapamil, then 1211

Fiber #3: Verapamil, 1211, then 10^{-6} M isoproterenol

Cyclic AMP and Cyclic GMP Assays

Each Purkinje fiber will be assayed in duplicate for cAMP and cGMP using radioimmunoassay techniques. Each fiber will be homogenized in cold trichloroacetic acid following the electrophysiology experiments. The following radioimmunoassay for cAMP and cGMP will be followed. The TCA-Purkinje fiber homogenate will be centrifuged. The precipitate may be used for protein determination. The supernatant will be adjusted for pH. TCA will be extracted with ethyl ether several times, then the ether will be aspirated off. Acetylation of the sample will be achieved by adding triethylamine and acetic anhydride in a fume hood. An amount of sample, standard or black will be placed in a glass test tube in duplicate. An amount of ^{125}I-2'-O-succinyltyrosine methyl ester-cAMP/cGMP will be added to the tube. After antiserum and buffer are added to each tube, they will be incubated over night at 0-4°C. The next day, bound and free ^{125}-I-S-TME-cAMP/cGMP will be separated by ammonium sulphate precipitation or charcoal adsorption. Following this step, each tube will be counted in

a Gamma counter or scintillation counter. Computer or calculator analysis of radioactivity counts will indicate the concentration of cAMP or cGMP in each tube.

Preliminary results

At a concentration of 10^{-6} M, isoproterenol causes an approximate two-fold increase in Purkinje fibers' cAMP content. Likewise, 1211 increase cAMP content and appears to augment the increase due to isoproterenol when both are administered together. Also, it appears that the 1211 stimulated increase in cAMP content is not blocked by atenolol, but by isoproterenol stimulation. Completion of these studies is underway and it appears that they may well provide a partial explanation of 1211 cardiac sensitization.

TABLE I

Isoproterenol Dose Response

	HEART RATE (beats/min)	SYSTOLIC BLOOD PRESSURE (mmHg)	DIASTOLIC BLOOD PRESSURE (mmHg)
Control (iso.)	143.33 ± 10.27	139.67 ± 2.96	104.33 ± 3.31
1 µg/kg (iso.)	194.67 ± 8.14	109.67 ± 8.29	53.67 ± 6.28
3 µg/kg (iso.)	220.00 ± 12.25	111.50 ± 6.98	60.25 ± 8.60
5% 1211	165.33 ± 19.55	141.67 ± 4.39	104.00 ± 2.97
.01 µg.kg (iso.)	175.00 ± 17.56	141.00 ± 6.64	104.75 ± 4.13
.02 µg/kg (iso.)	170.67 ± 25.83	135.67 ± 6.98	109.33 ± 8.19
.04 µg/kg (iso.)	176.67 ± 21.86	131.67 ± 7.51	99.67 ± 7.22
.08 µg/kg (iso.)	180.00 ± 00.00	118.50 ± 6.50	92.00 ± 8.00

TABLE II

Atenolol - 1211 Dose Response

	HEART BEAT (beats/min)	SYSTOLIC BLOOD PRESSURE (mmHg)	DIASTOLIC BLOOD PRESSURE (mmHg)
Control w/o Atenolol	160.83 ± 9.35	160.00 ± 2.64	123.67 ± 3.20
Control w/Atenolol	122.50 ± 3.59	170.00 ± 3.63	130.83 ± 3.16
2% 1211 (45.64 ± 0.82 mg/ml)	122.50 ± 3.09	162.00 ± 2.11	124.50 ± 3.94
1 µg/kg isoproterenol	127.50 ± 3.10	134.50 ± 6.61	86.33 ± 9.70
5% 1211 (93.22 ± 3.20 mg/ml)	126.67 ± 4.22	158.50 ± 5.09	119.50 ± 2.01
1 µg/kg isoproterenol	136.67 ± 5.11	131.67 ± 2.69	77.33 ± 5.26
10% 1211 (155.08 ± 9.65)	127.50 ± 5.12	151.50 ± 2.01	115.17 ± 1.30
1 µg/kg isoproterenol	181.67 ± 10.46	126.83 ± 3.12	70.50 ± 4.70
20% 1211 (272.13 ± 25.32 mg/ml)	132.50 ± 6.16	117.00 ± 3.29	89.50 ± 2.66
1 µg/kg isoproterenol	185.00 ± 12.91	100.83 ± 4.64	75.50 ± 2.95

Figure 1

Fiber stretch. (A, B) control; (C, D) 20% stretch; (E, F) 20% stretch plus 1211 at flow of 20 ml/min; (G, H) 20% stretch plus 1211 at flow of 40 ml/min; (I) 20% stretch plus 1211 at flow of 60 ml/min.

Figure 2

Phenylephrine and 1211. (A) control; (B, C, D) phenylephrine at 10^{-9} M, 10^{-8} M and 10^{-7} M; (E) control after washout, (F) 1211 at flow of 40 ml/min; (G, H, I) 1211 at flow of 40 ml/min plus phenylephrine at 10^{-9} M, 10^{-8} M and 10^{-7} M; (J) washout of 1211 and phenylephrine.

Figure 3

cAMP and 1211. (A, B) control; (C, D) $3x10^{-4}$ M dibutyryl cAMP; (E, F) $3x10^{-3}$ M dibutyryl cAMP; (G, H) 1211 at flow of 20 ml/min plus dibutyryl cAMP at $3x10^{-3}$ M; (I, J) 1211 at flow of 40 ml/min plus dibutyryl cAMP at $3x10^{-3}$ M; (K) 1211 at flow of 60 ml/min plus dibutyryl cAMP at $3x10^{-3}$ M; (L) washout.

Figure 4

Effects of 1211 on slow channel AP sequential additions. (A) control; (B) depolarization by 16 mM K^{+}; (C) elevated Ca^{++}, 5.4 mM; (D) 10^{-7} M isoproterenol; (E) 1211 at flow of 20 ml/min; (F) 1211 at flow of 40 ml/min; (G) 1211 at flow of 60 ml/min; (H) atenolol at 10^{-5} M.

Figure 5

Cardiac sensitization by 5% 1211. (A) control; (B) 1 µg/kg isoproterenol; (C) 3 µg/kg isoproterenol; (D) 5% of 1211; (E, F, G, H) 5% 1211 plus isoproterenol at .01, .02, .04 and .08 µg/kg. ECG is displayed in upper part of each frame and arterial BP in lower.

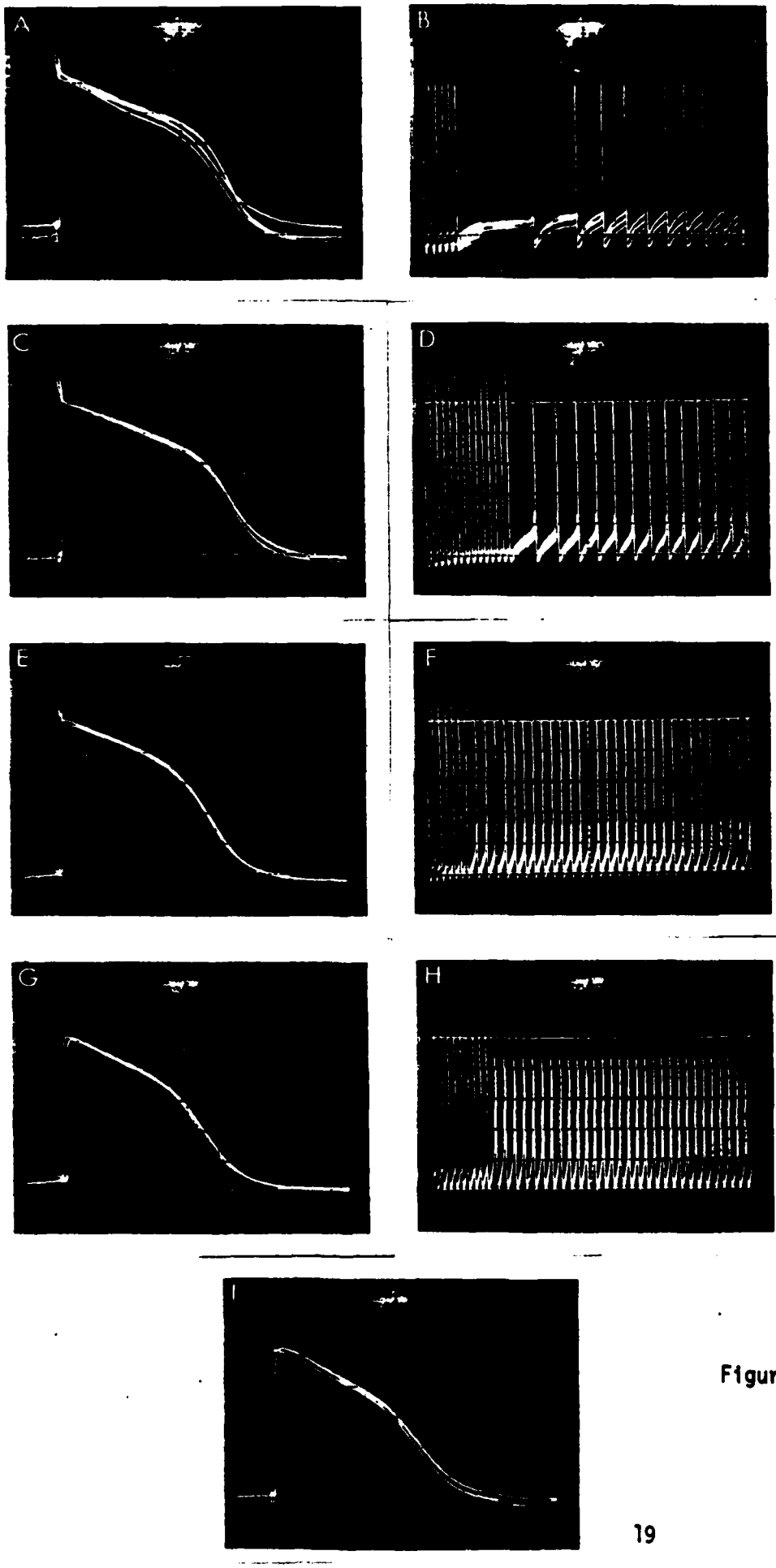
Figure 6

Effects of 1211 on cardiac rhythm in presence of beta blockade. (A) control;(B, C, D, E,) 1211 at 2, 5, 10 and 20% of inspired air; (F) control plus atenolol, 4 mg/kg; (G, H, I, J) atenolol and 1 µg/kg challenge of isoproterenol at 2, 5, 10 and 20% 1211 in inspired air.

Figure 7

1211 blood superfusion. Upper panel, Purkinje fiber action potential. Lower panel, ECG, left ventricular pressure, arterial pressure. (A) control in blood; (B) 2.5 min. after .8 µg/kg isoproterenol;

(C) 5% 1211; (D) 2.5 min after .4 μg/kg isoproterenol in presence of 5% 1211; (E) 2.5 min after .4 μg/kg isoproterenol in presence of 5% 1211 and 4 mg/kg atenolol.



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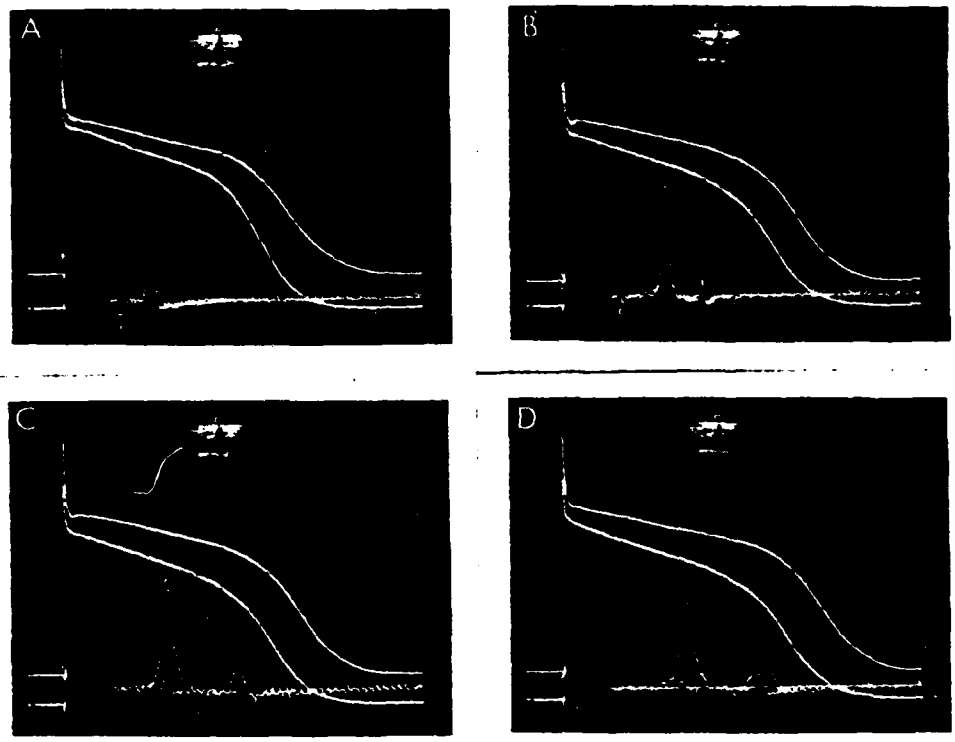

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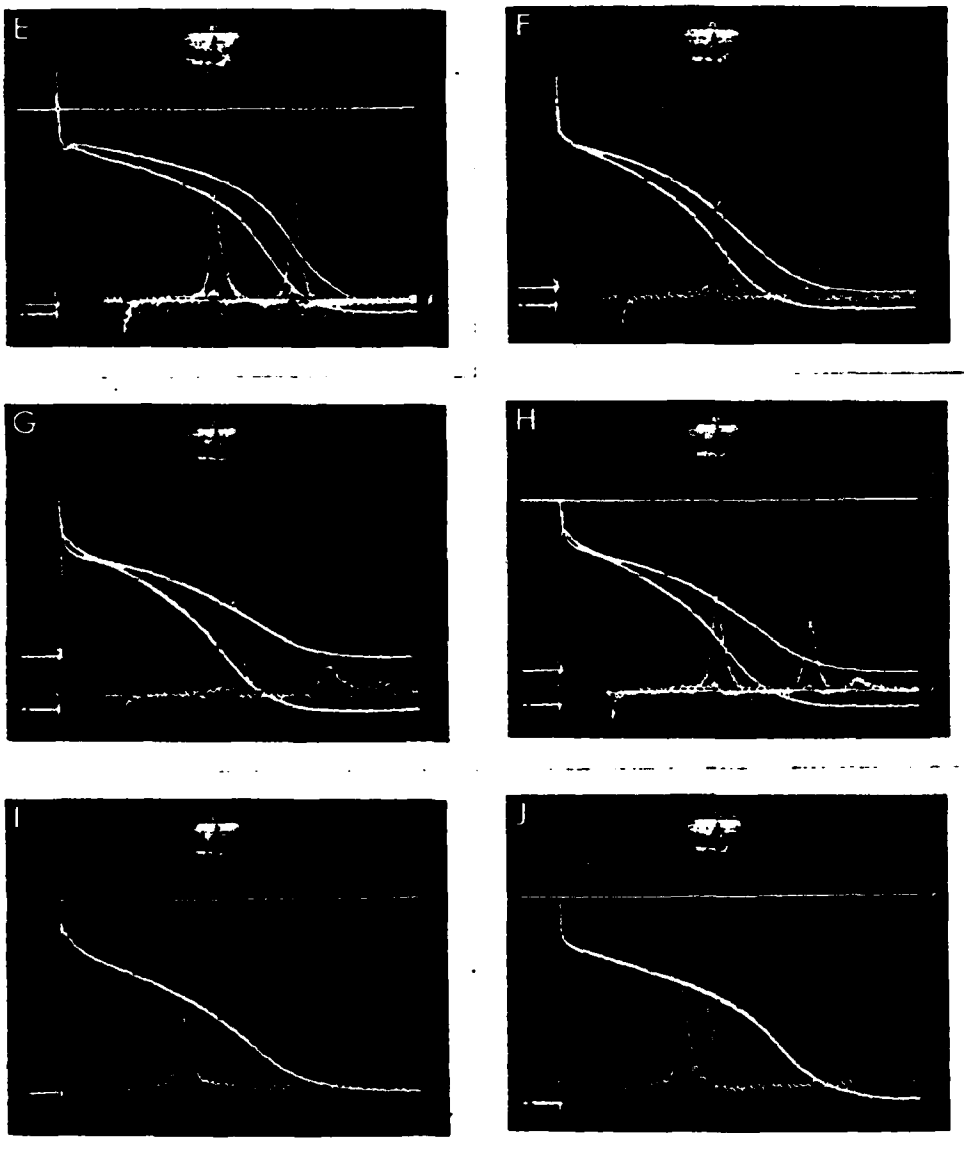

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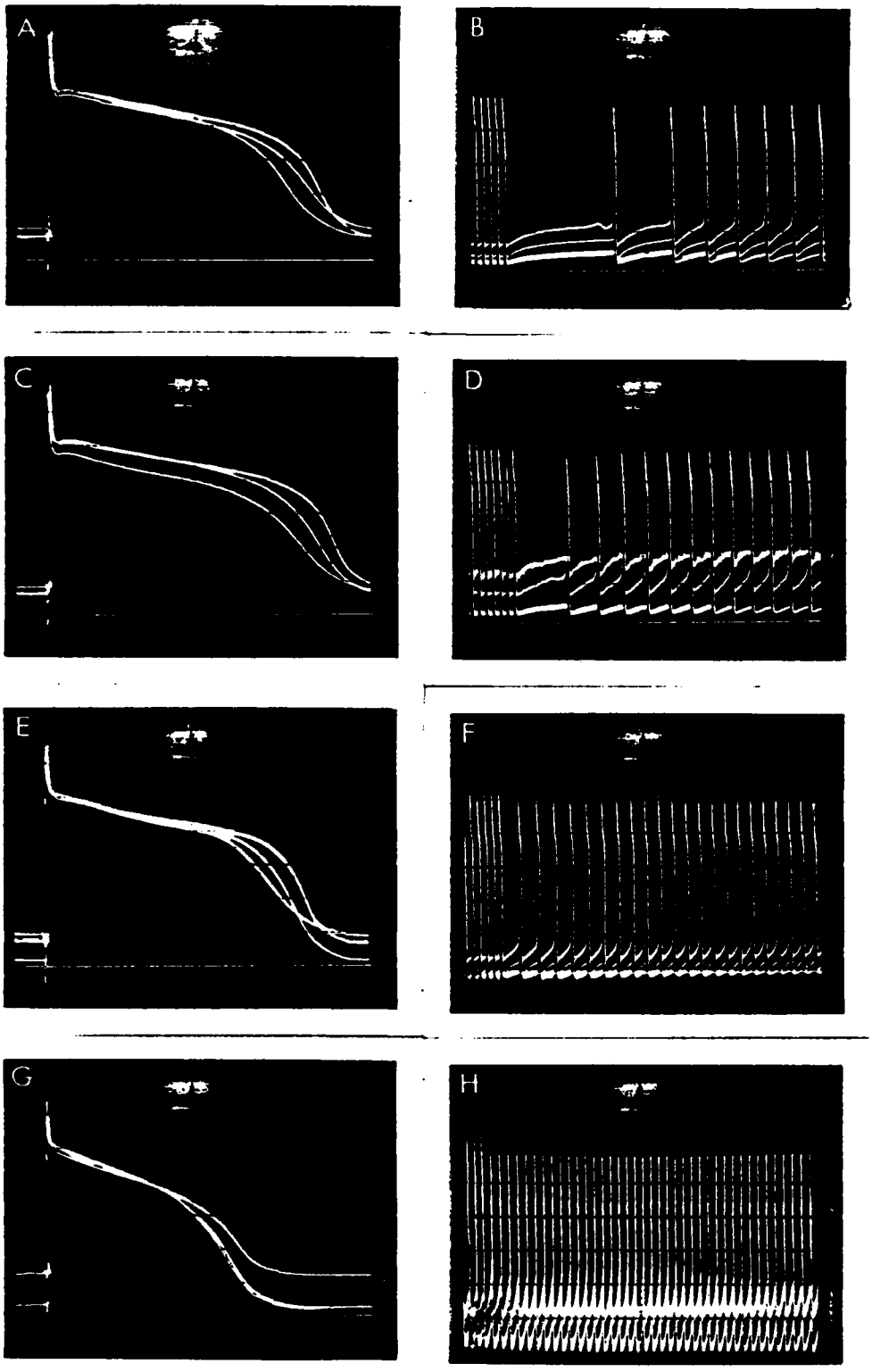
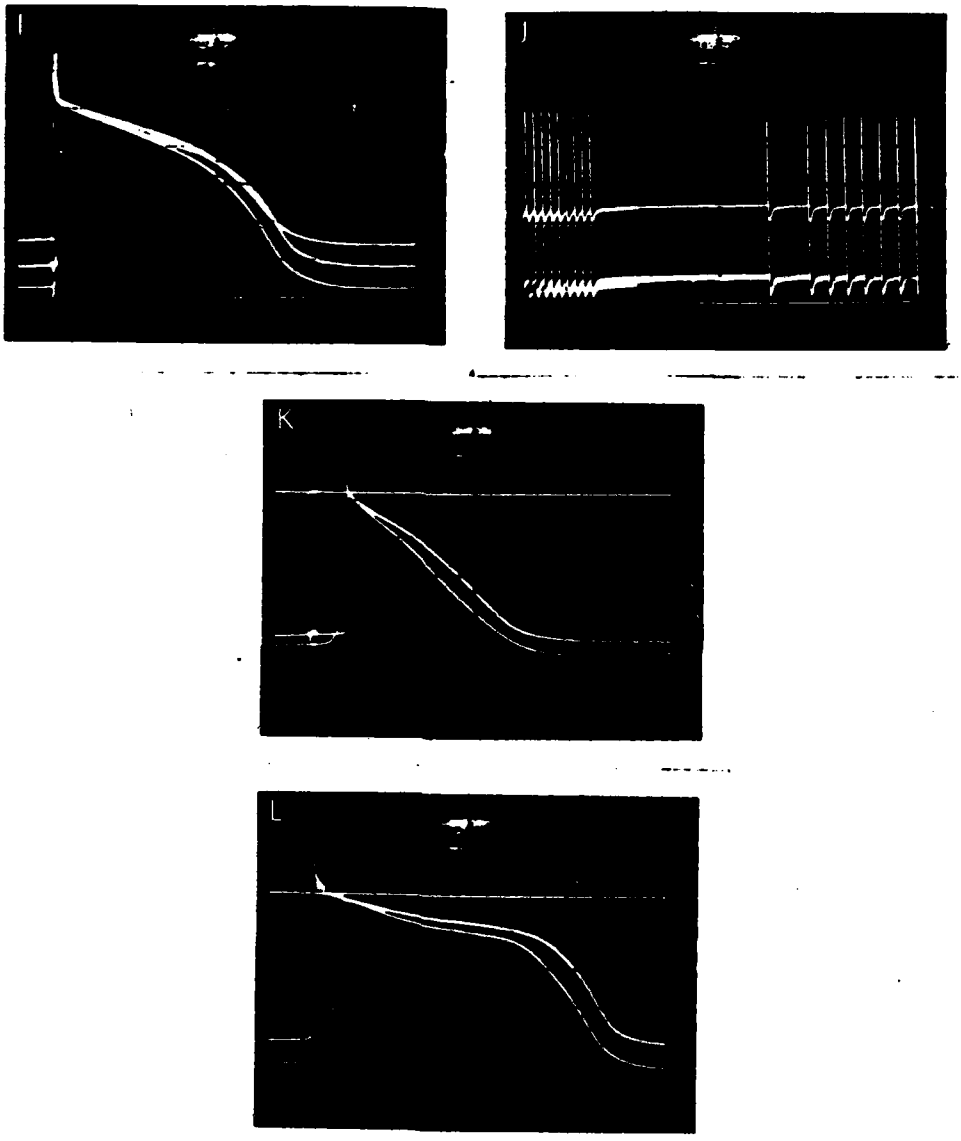


Figure 3



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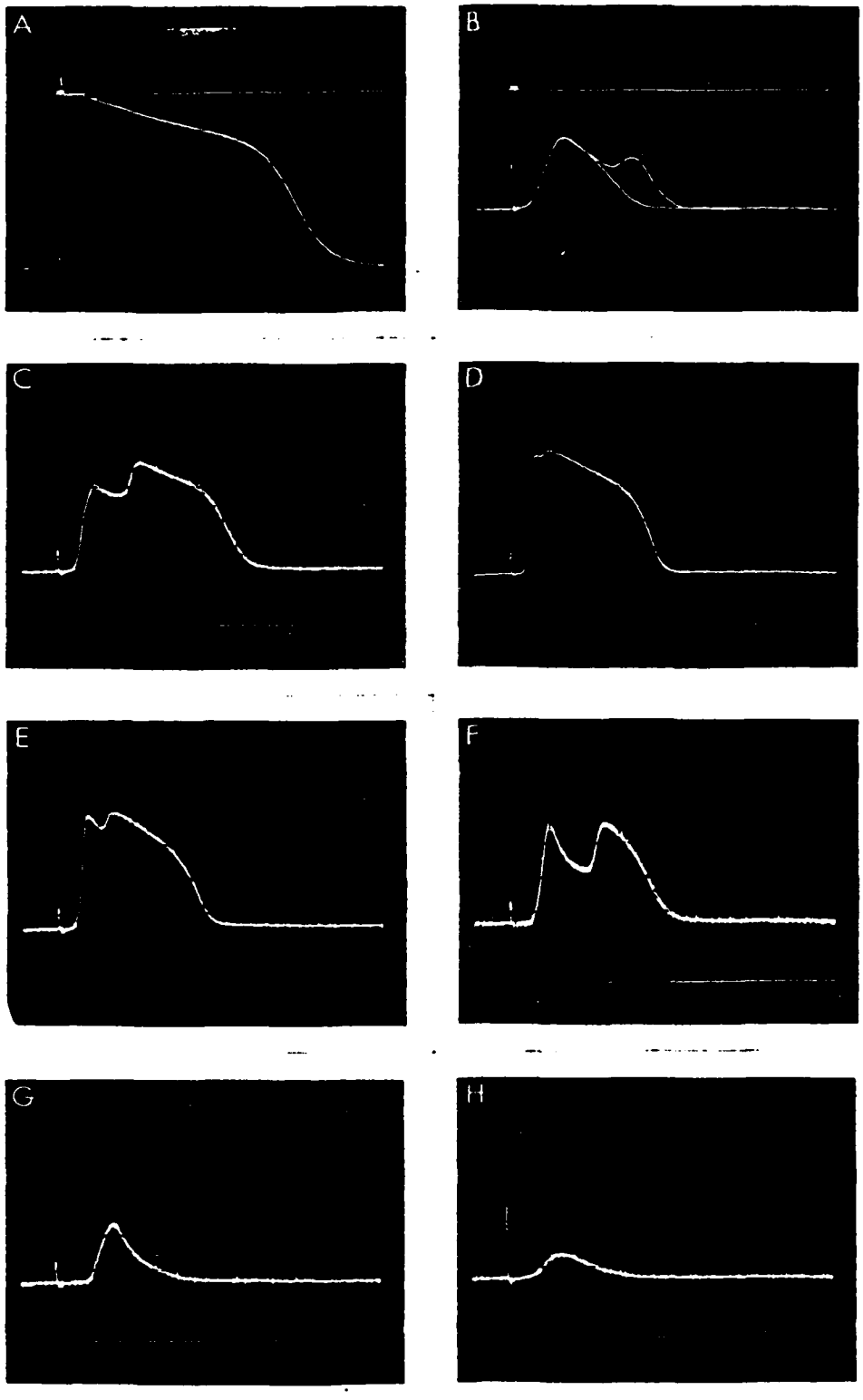

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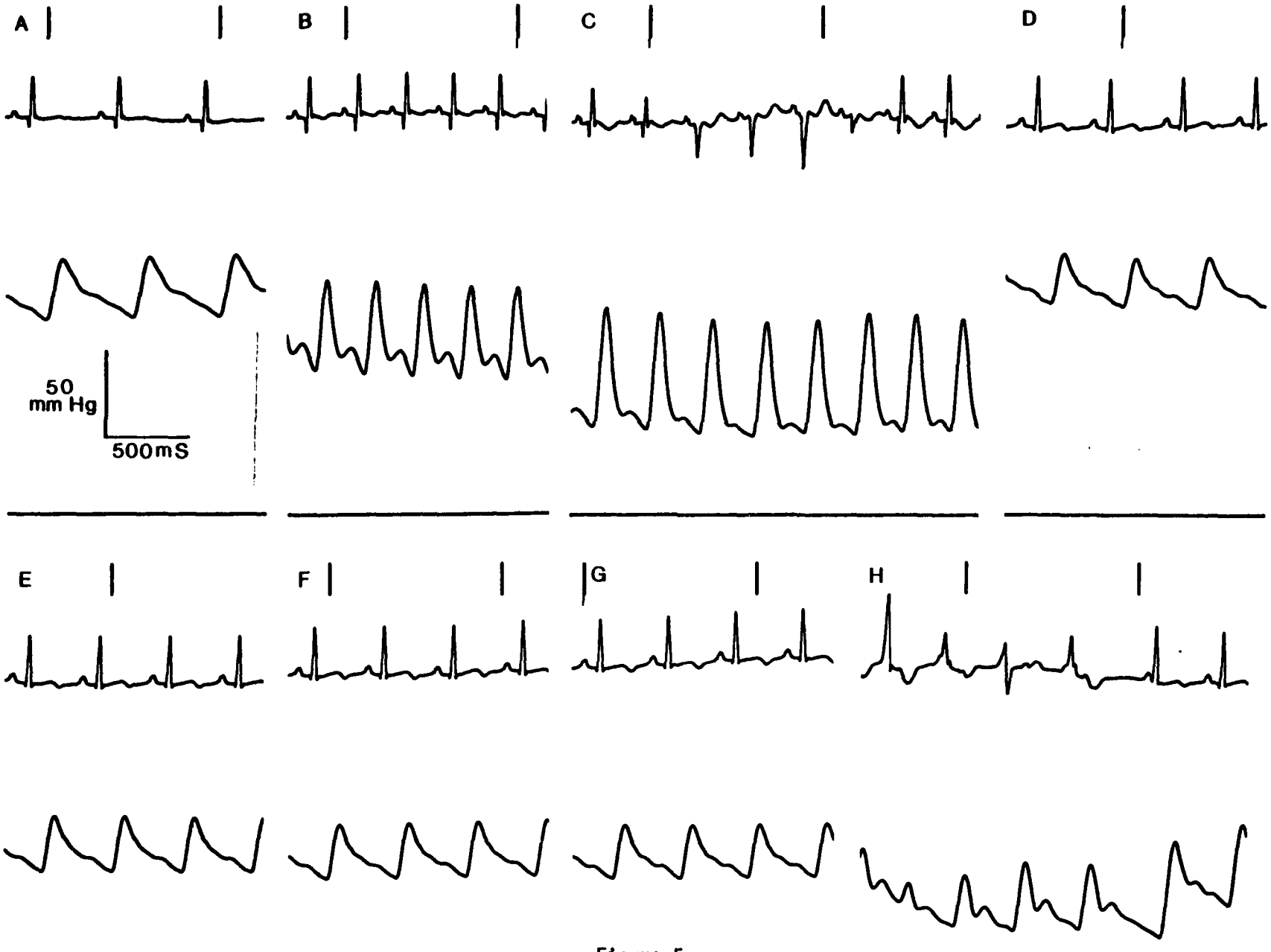

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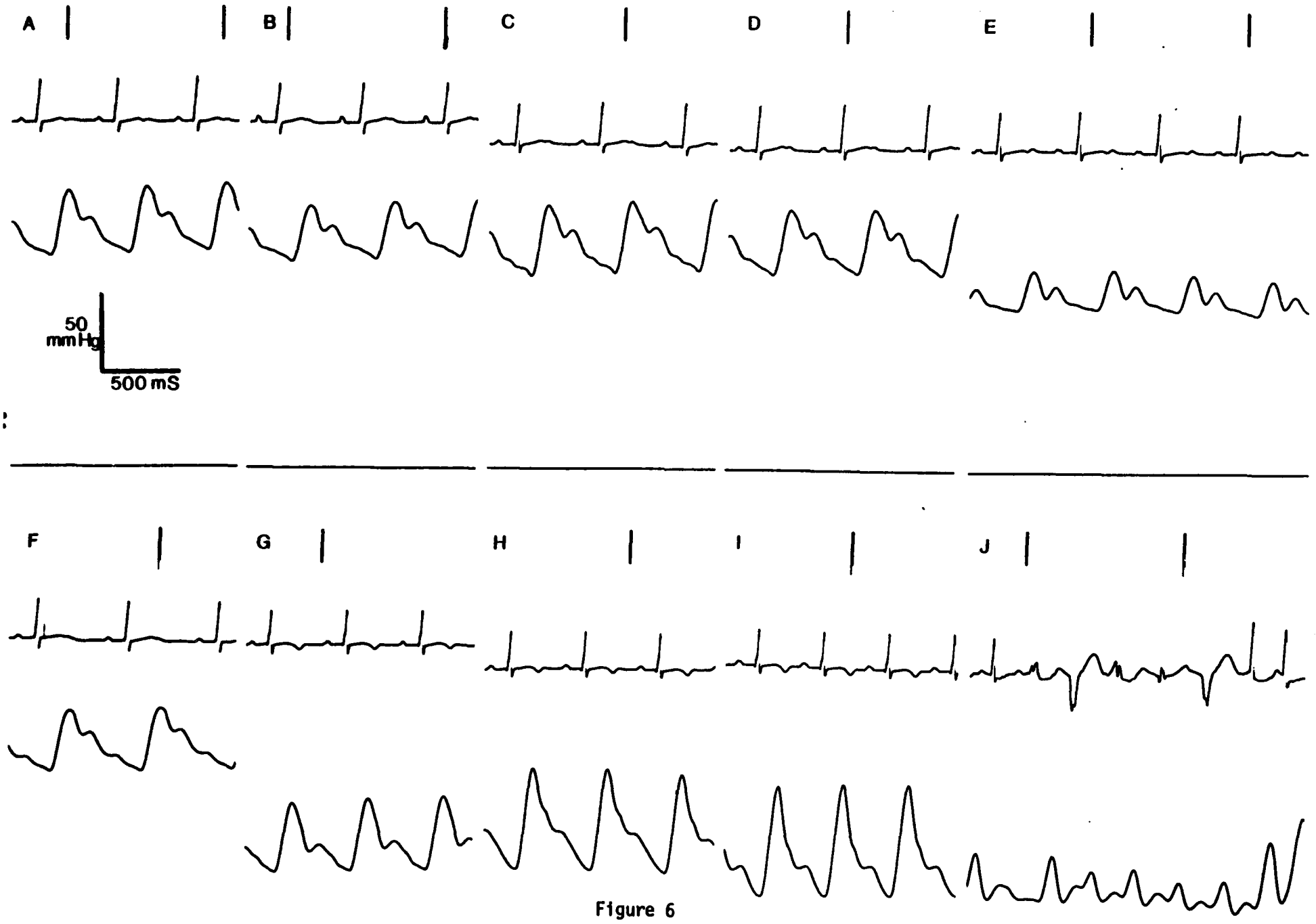
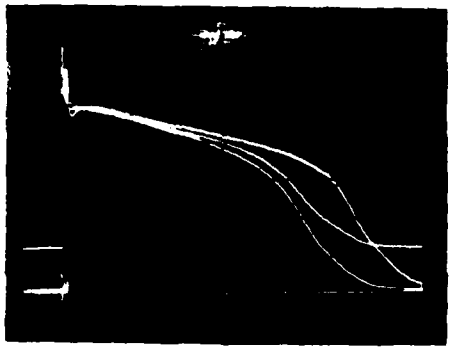


Figure 6

A



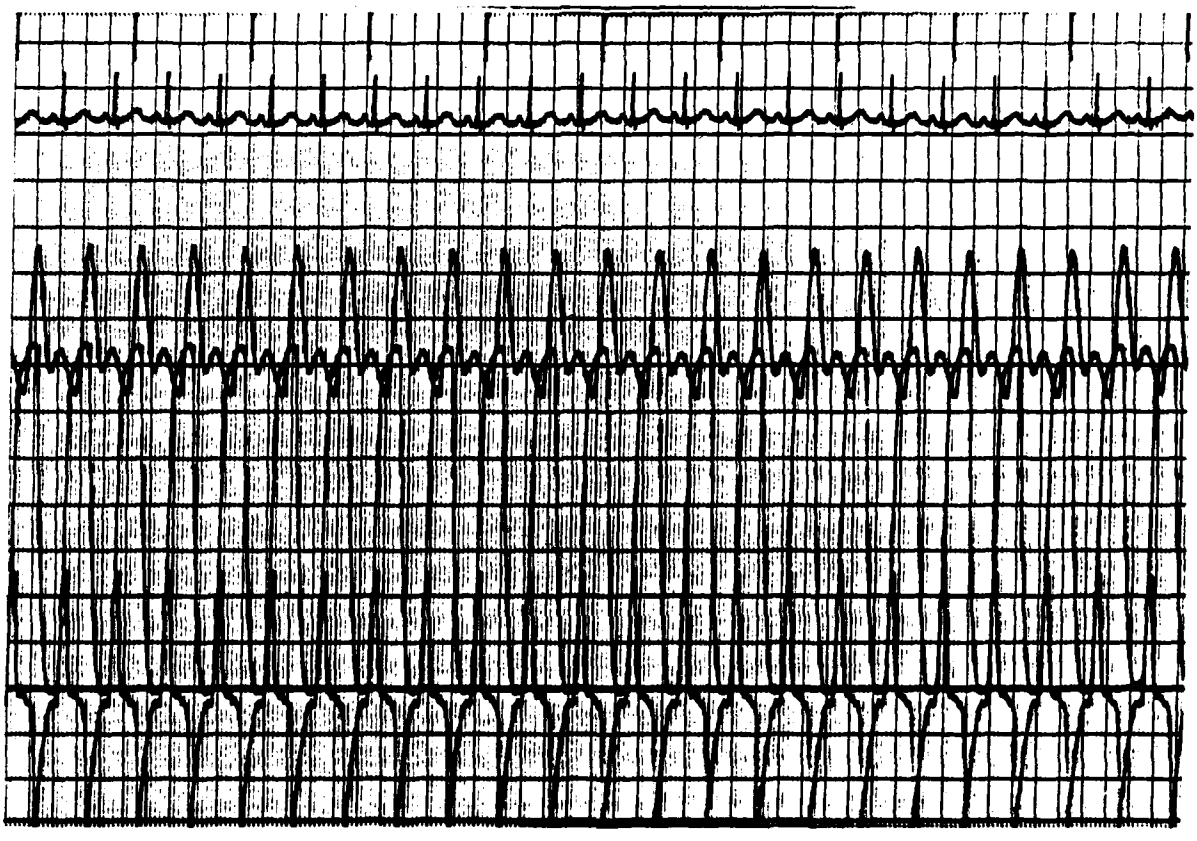
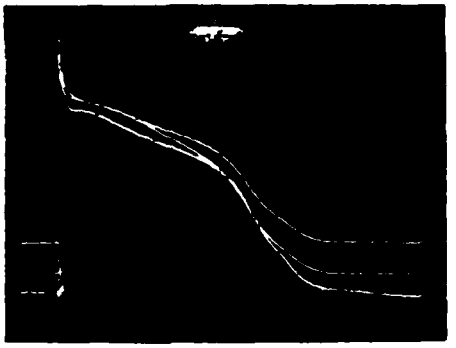


Figure 7

B



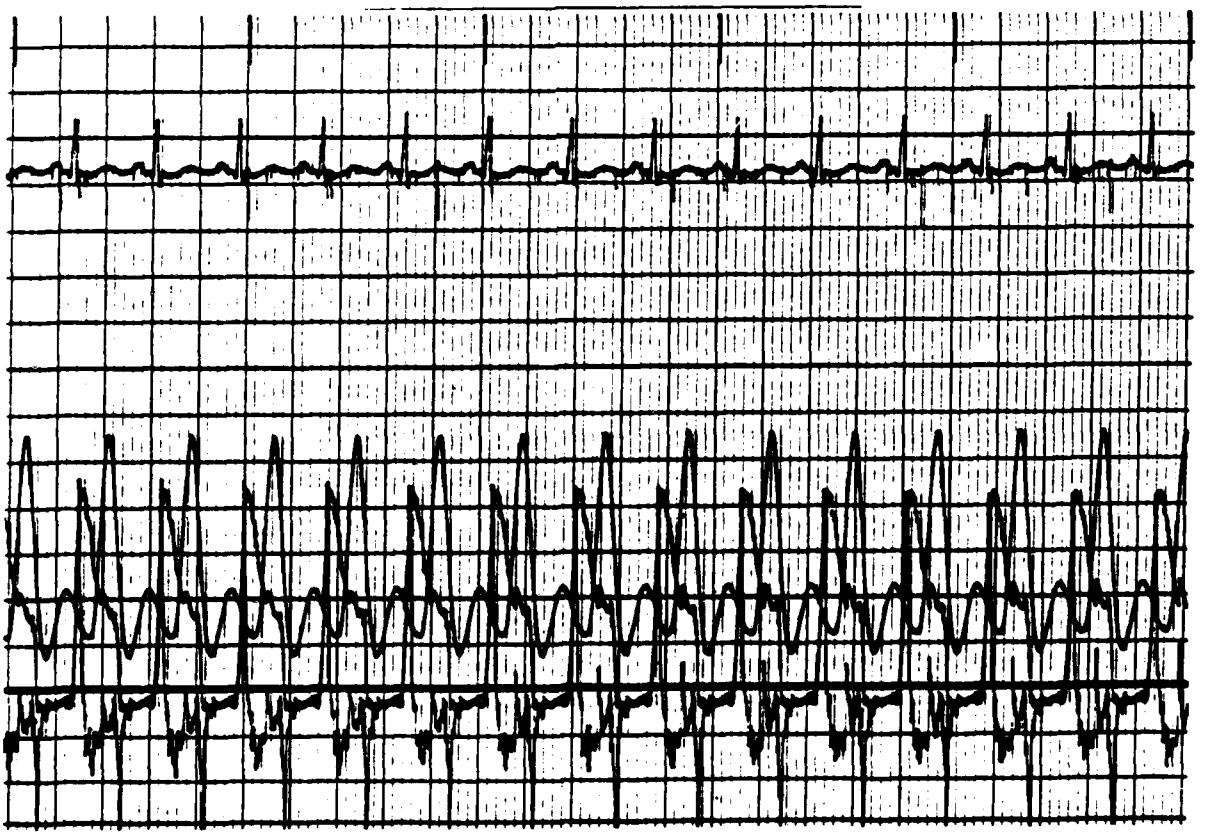


Figure 7 (continued)

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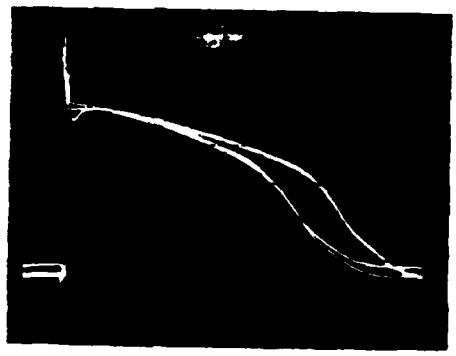


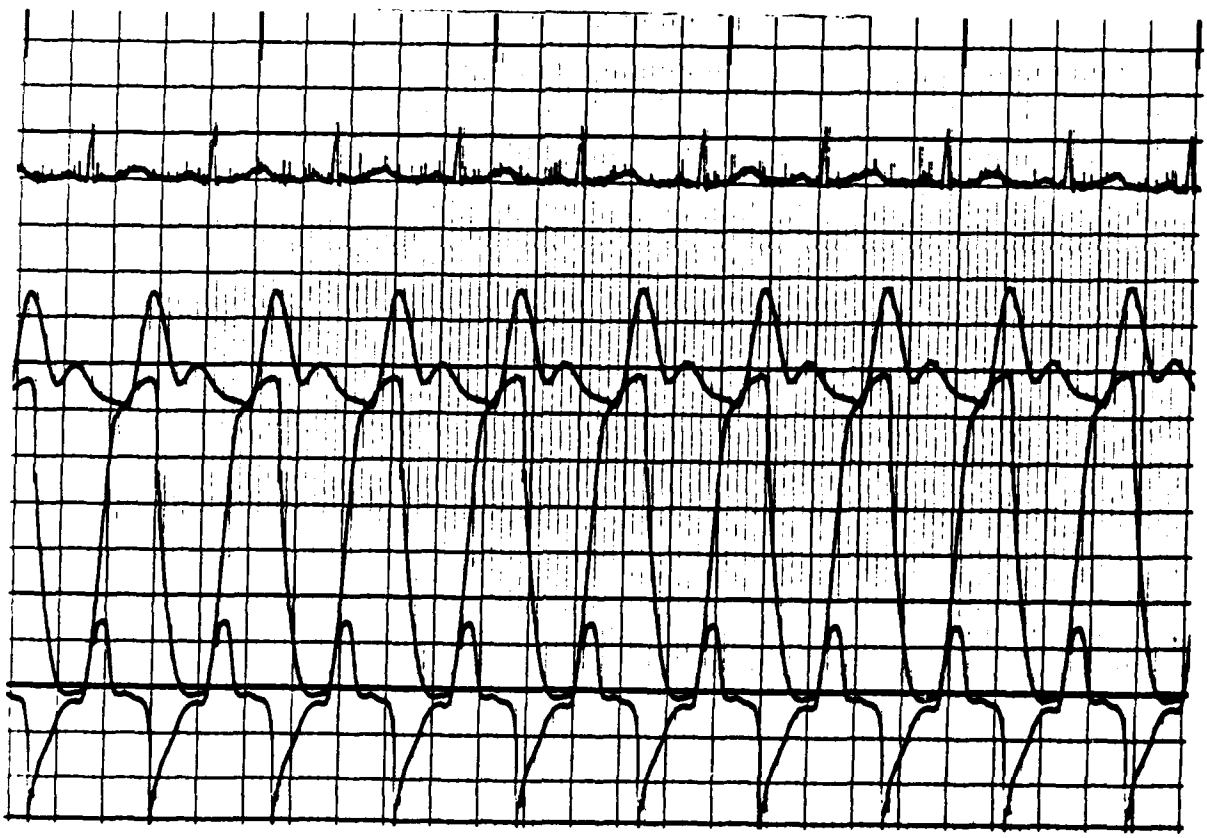
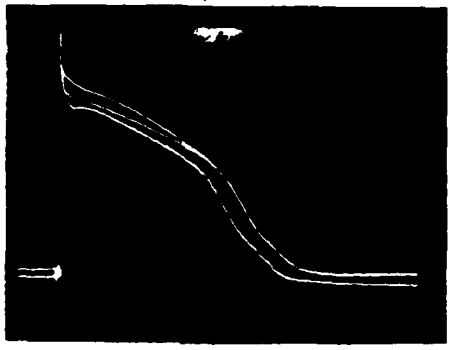


Figure 7 (continued)

D



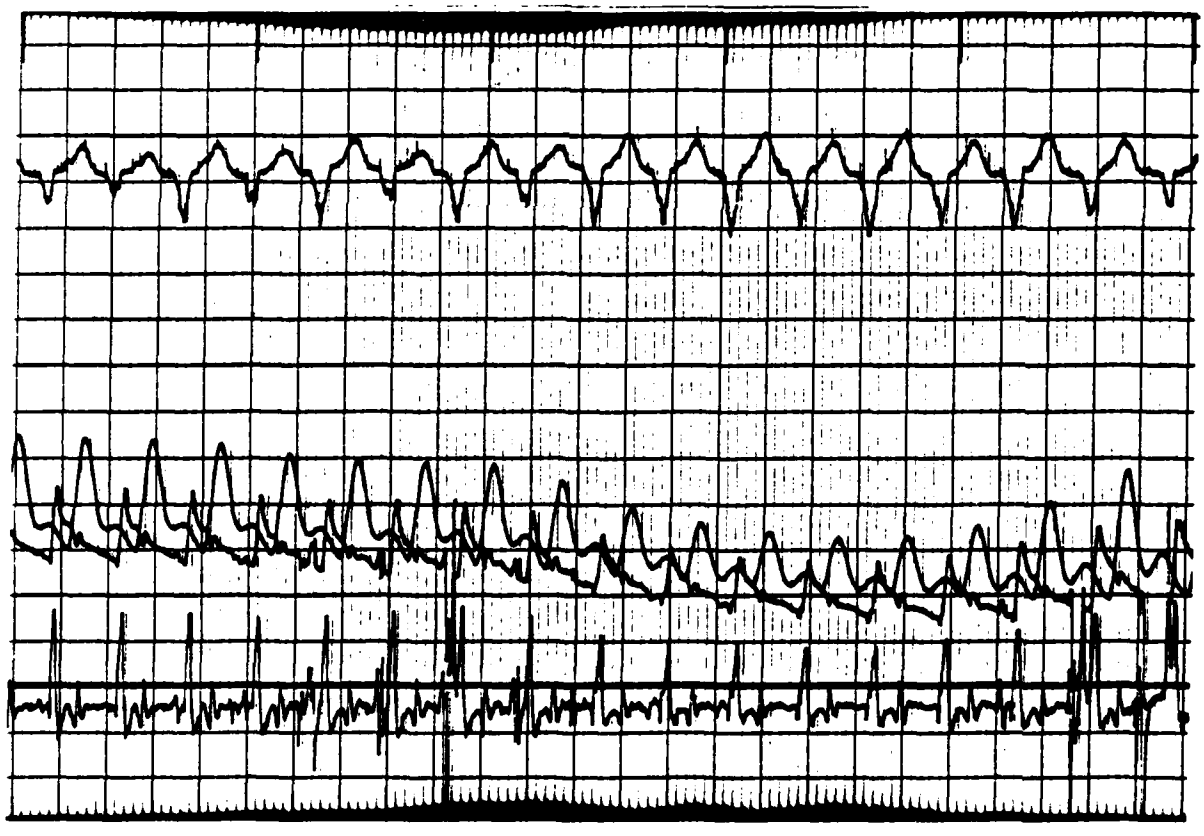
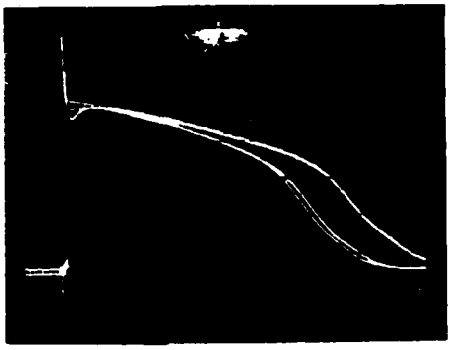


Figure 7 (continued)

E



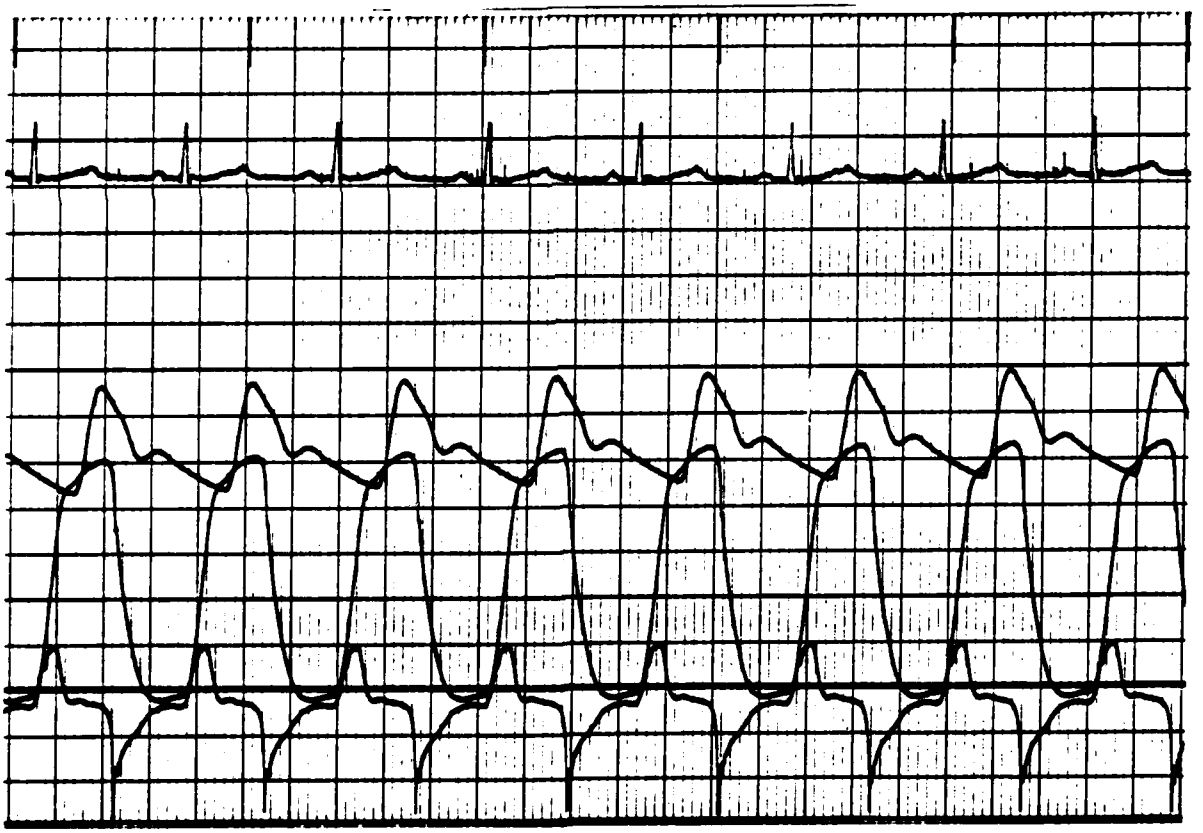


Figure 7 (continued)

PUBLICATIONS

The electrophysiology studies are near completion and it is anticipated that these will be submitted as a series of two or three papers to a major journal in the area of either toxicology or cardiology. The cardiac sensitization by 1211 to isoproterenol in conscious dogs is in preparation for submission for publication.

PROFESSIONAL PERSONNEL

S. M. Strauch, Ph.D.: Principal Investigator

J. L. Sally, M.Sc.: Research Associate

W. W. Muir, D.V.M., Ph.D.: Consultant

G. Peterson: Graduate Research Assistant

H. B. Ernest: Graduate Research Assistant

INTERACTIONS

(A) Results of the first year of work was presented at:

Review of Air Force Sponsored Basic Research in Environmental Toxicology, Columbus OH, 2-3 June 1981.

Exchange of ideas and discussion of research with colleagues at The Ohio State University, College of Medicine and College of Veterinary Medicine who participate in cardiovascular, electrophysiology and toxicology discussion groups and journal clubs

(B) Consulted with:

COL Roger Inman and Mr. Jeff Fisher, AMRL/THE regarding electrophysiology instrumentation for studying the effects of toxicants on fish activity. Met with the above on 2/3/82 in Columbus, OH, and on 5/3/82 at WPAFB, Dayton, OH.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